TITLE: Perioperative oxidative stress: the unseen enemy

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ABSTRACT

Reactive oxygen species (ROS) are essential for cellular signalling and physiological function. An imbalance between ROS production and antioxidant protection results in a state of oxidative stress (OS), which is associated with perturbations in redox regulation, cellular dysfunction, organ failure and disease. The pathophysiology of OS is closely interlinked with inflammation, mitochondrial dysfunction and, in the case of surgery, ischemia/reperfusion injury. Perioperative OS is a complex response that involves patient, surgical and anaesthetic factors. The magnitude of tissue injury inflicted by the surgery affects the degree of OS, and both duration and nature of the anaesthetic procedure applied can modify this. Moreover, the inter-individual susceptibility to the impact of OS is likely to be highly variable and potentially linked to underlying comorbidities. The pathological link between OS and postoperative complications remains unclear, in part due to the complexities of measuring ROS and OS-mediated damage. Exogenous antioxidant use and exercise have been shown to modulate OS and may have potential as counter-measures to improve postoperative recovery. A better understanding of the underlying mechanisms of OS, redox signalling and regulation can provide an opportunity for patient-specific phenotyping and development of targeted interventions to reduce the disruption that surgery can cause to our physiology. Anesthesiologists are in a unique position to deliver countermeasures to OS and improve physiological resilience. To shy away from a process so fundamental to the welfare of these patients would be foolhardy and negligent, thus calling for an improved understanding of this complex facet of human biology.

GLOSSARY OF TERMS AND ABBREVIATIONS

$^{\bullet}$NO – Nitric oxide

$^{\bullet}$OH - Hydroxyl radical

8-OHdg - 8-hydroxy-2’-deoyguanosine

AAA – Abdominal aortic aneurysm

BAL- Bronchial alveolar lavage

BAP - Biological antioxidant potential

CABG – Coronary artery bypass graft

CAT- Catalase

CVD- Cardiovascular disease

DAMPs - Damage associated molecular patterns

ETC – Electron transport chain

GA – General anaesthesia

GPx – Glutathione peroxidase

GSH - Reduced glutathione

GSSG-Glutathione disulfide

H_2O_2 - Hydrogen peroxide

HNE – 4-Hydroxynonenal

IMM – Ineer mitochondrial membrane

IP – Ischemia perfusion

IR – Ischemia reperfusion

IRI - Ischemia reperfusion injury

MDA - Malonaldehyde

MPO - Myeloperoxidase

mtDNA – Mitochondrial DNA

N_2O – Nitrous oxide

NF-κB - Nuclear factor-κB

NLR-NOD like receptors

NLRP3 - Leucine Rich Repeat And Pyrin-Domain Containing-3

NOD - Nucleotide-binding oligomerizations domain

NOX – NADPH oxidase

$O_2^{\cdot -}$ - Superoxide

OLV – One lung ventilation

$ONOO^-$ - Peroxynitrite

ORP – Overall redox potential

OS - Oxidative stress

OXPHOS - Oxidative phosphorylation

POC – Point of care

PPAR-γ- Peroxisome proliferator activated receptor-γ

RA – Regional anesthesia

ROS - Reactive oxygen species

RNS – Reactive nitrogen species

RSS – Reactive sulfur species

SOD – Superoxide dismutase

TIVA – Total intravenous anethesia

TLR – Toll like receptors

TNF – Tumour necrosis factor

WHO – World Health Organisation

INTRODUCTION

Life evolved in an environment devoid of oxygen, and it was not until the appearance of photosynthesis that oxygen began to accumulate in the Earth's atmosphere, radically altering the trajectory of evolution.[1] The key inflection point in the story of life on Earth was the joining of two ancient single-celled organisms (a small obligate aerobe and a larger anaerobe) to create what became the forerunner of the eukaryotic cell. The aerobic bacteria had evolved a process to use oxygen as an electron acceptor and unlock energy from carbon compounds. They were the ancestors of the mitochondria, and the energetic process was oxidative phosphorylation (OXPHOS). The advantage of this biological union for the anaerobic bacteria was protection from the rising concentration of oxygen in the Earth's atmosphere 2.5 billion years ago. In exchange, the recipient cell and every one of its descendants gained an in-house, oxygen-fired power plant. Oxygen is a relatively reactive molecule, which makes it a high-risk choice for an electron acceptor in an energetic pathway. It also explains the paradox that although it is essential for aerobic life, excess oxygen can have devastating effects on the framework and function of cells, through the generation of reactive oxygen species (ROS) that are produced in cellular metabolism and OXPHOS. Reduction/oxidation (redox) reactions are fundamental to biochemical reactions driving the cellular machinery. Cells must keep ROS production under control to maintain harmony, and disruption of the fine balance between formation, scavenging and safe deposition can create a state of oxidative stress (OS). We cannot live without oxygen, too much can harm us.

While this may seem a million miles away from the setting of an operating room, anesthesiologists have a duty to optimise patients in long-term health and well-being. Arguably, this role includes minimising exposure to OS in a similar way to which we now try to avoid an excessive perioperative inflammatory response. Preoperatively OS has been implicated in the pathogenesis of multiple disease entities[2], intraoperatively OS underlie the mechanism of the acute phase response during injury and stress[3], and postoperatively measures of OS have been correlated to complications after surgery[4], which may have potential to becoming risk stratifying biomarkers. We often assume what we cannot see will not harm us; however, with OS this is clearly *not* the case. Multiple avenues are being explored to understand and reduce perioperative OS, in order to prevent harm from this silent enemy.

REACTIVE OXYGEN SPECIES, REDOX REGULATION AND OXIDATIVE STRESS

In humans, ATP is primarily derived from the OXPHOS process taking place in the inner mitochondrial membrane (IMM). Oxygen, delivered to our cells through a combination of convective and diffusive processes, acts as an electron acceptor in a series of reduction/oxidation (redox) reactions that occur across five sophisticated protein structures (named complex I to complex V) in the electron transport chain (ETC). Energy released during the flow of electrons through these complexes is used to move protons against an electrochemical gradient across the IMM. The ensuing build-up of potential energy (in the form of a pH and electrochemical gradient) is then used to create ATP as protons flow back across the membrane via ATP synthase.[5] At complexes I and III a small proportion of electrons are uncoupled from the ETC and oxygen is reduced to superoxide anions ($O_2\cdot^-$).[6] The addition of an unpaired electron to oxygen makes this intermediate highly reactive; subsequent additions of electrons give rise to hydrogen peroxide (H_2O_2) and then to the hydroxyl radical (·OH), other members of the ROS family (information box 1). The production of these ROS is part of normal cellular biology and oxidative metabolism. Several other cellular sites have been identified as centres of ROS production, residing in redox systems of enzymes within cellular organelles and the cytosol; in general, they are classified into mitochondrial and extra-mitochondrial sources (Figure 1).[7] Some of the key redox enzymes involved are summarised in Figure 2. At physiological concentrations, ROS serve numerous essential roles in cell signalling, immunity, differentiation and apoptosis.[8] Cell and tissues have a multi-layered innate defence system against excessive build-up of ROS, primarily in the form of ROS-metabolising enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and small-molecule antioxidants.[9] Many non-enzymatic antioxidants are dietary in nature, and include α-tocopherol, ascorbic acid (vitamins E and C), and ß-carotene, whereas the lipophilic co-enzyme Q_{10} (ubiquinol), which plays an important role in the mitochondrial electron transport chain (ECT), is also produced endogenously.[10,11] Redox reactions are present in almost all aspects of life, redox regulation and signalling balances the body’s internal state of pro-oxidant and antioxidant reactions. Physiological levels of ROS are normally kept in check by these homeostatic processes, but disturbances can lead to increased peak concentrations of ROS and a state of pathological

OS.[9] This has multiple consequences: it can result in oxidative modification and degradation of nucleic acids, proteins, and lipids,[2] compromising the infrastructure of life itself. Lipid peroxidation products play a key role in this setting due to their self-perpetuating chain reactivity,[12] with mitochondria proposed to be at the centre of their generation while simultaneously being the targets that lead to interference in their metabolism.[13,14] Concomitantly, their reaction with protein thiols modifies the way cells adapt to stress.[15] OS can change the way different cells and cellular organelles communicate with each other, perturbing the flow of communication within and between cells and organs via an interconnected redox system.[16] In an analogy to our genetic code there exists a ‘redox code’, a set of principles according to which redox changes throughout the body are organised.[17] Furthermore, a family of N-based molecules called reactive nitrogen species (RNS) exist, which originate from the activity of nitric oxide synthase (NOS). Its most prominent member is peroxynitrite ($ONOO^-$), a potent pro-oxidant derived from the reaction of nitric oxide ($\cdot NO$) with superoxide, which is formed particularly under inflammatory conditions.[18] Both ROS and RNS can target cysteine thiols leading to a variety of oxidative changes, which can affect thiol-based signalling and the function of numerous membrane proteins and cytosolic enzymes. In addition, various reactive sulfur species (RSS) exist,[19] with both pro-oxidant and antioxidant effects some of which are closely linked to mitochondrial function.[20] The interactions of ROS, RNS, RSS and their downstream biological targets are not fully understood, and a novel concept of the ‘reactive species interactome’ has been formulated to further elucidate the mechanistic relationships.[21] For the purpose of this review, however, we shall concentrate on the effects of ROS and their contributions to OS.

SURGERY AND OXIDATIVE STRESS

Surgery is an acute event that not only results in localised tissue injury but also systemic dysfunction. Inflammation and ischemia/reperfusion (IR) injury are two important components in this process, and ROS play a role in their modulation.[22] Surgery classically results in a 'stress response' driven by endocrine changes that lead to metabolic sequelae.[23] Cytokines play a key role, driving the ebb and flow of the inflammatory response.[24] What is less well described is the close interplay this stress response has with OS, which directly links mitochondrial function to the effects of surgery. ROS produced by mitochondria have been shown to enhance inflammatory processes through the activation of cellular receptors, transcription factors and the formation of the inflammasome, via the release of mitochondrially mediated damage associated molecular patterns (DAMPs) (Figure 3).[25]

IR injury (IRI) is classically associated with organ transplantation, cardiac, and hepatic surgery, along with the use of limb tourniquets and vascular clamps. During the ischemic phase of IRI, anaerobic respiration prevails, leading to a state of acidosis and ATP depletion; this is accompanied by the accumulation of reduced cofactors in the mitochondrial ETC. The reduced availability of energy limits ion pump function in cell membranes, causes calcium overload, eventually cell death. Extracellular ATP release[26] in conjunction with the release of pro-inflammatory markers, sets a stage for an oxidative burst during the reperfusion phase, when paradoxically the re-introduction of oxygen causes the release of ROS, OS and further tissue damage.[27] The common enzymatic sources include xanthine oxidase (XO), NADPH oxidase (NOX), the mitochondrial ECT and uncoupled NOS.[28] Reperfusion is a highly dynamic response, and the accompanying injury can continue for days. The presence of ROS in the latter part of the recovery phase serves opposite roles to the acute phase, functioning as essential signalling molecules in post-reperfusion healing, through the stimulation of angiogenesis and tissue re-modelling.[27] The relationship between ROS, oxygen homeostasis and mitochondrial dysfunction is central to the pathological mechanism of perioperative OS. In addition, sustained OS also contributes to the development of a number of chronic diseases and frailty;[29] comorbidities that contribute to increased perioperative risk.

MEASURING OXIDATIVE STRESS

The detection and quantification of ROS in biological systems is challenging, due to their short-lived and highly reactive nature,[30] but also to the involvement of multiple cells/tissues in the whole-body, and their responses to injury. Electron paramagnetic resonance is considered the gold standard for ROS detection and the only technique that offers direct measurement of unpaired electrons, but signal detection is complex. Multiple alternative techniques have been developed to measure products of ROS-mediated damage. Analytical methods for quantification of these reaction products include immunoassays, liquid chromatography and mass spectrometry.[31,32] Stable end products of ROS damage to membrane lipids, cellular proteins and nuclear constituents include the lipid oxidation products malondialdehyde

(MDA), 4-hydroxynonenal (HNE) and F_2-isoprostanes (8-iso-prostaglandin-$F_{2\alpha}$); 8-hydroxy-2'-deoyguanosine (8-OHdg) and protein carbonyls, oxidation products of DNA and amino acid residues, respectively. Measuring endogenous antioxidant enzymes such as GPx, CAT and SOD as well as the change in the ratio of reduced/oxidized thiol (e.g. glutathione and cysteine) concentrations can also provide information about the overall oxidative burden, but there is no agreement on which marker is more useful and under what condition. Perhaps the greatest challenge to the interpretation of any of these readouts is their biological inter-connectedness and our limited understanding about redox regulation at the whole-body level.[21] Novel technologies are available that use a composite electrochemical readout of the overall redox potential (ORP), derivatives of reactive oxygen metabolites (dROMS) or biological antioxidant potential (BAP). Point of care (POC) systems now exists to provide rapid readings of OS from a small amount of blood. A growing body of work explores the application of these as a prognostic marker of disease progression and severity.[33–36] Since laboratory tests are expensive, lengthy and complicated techniques, the validation of POC measurements could bring the science of OS to the bedside.

PREOPERATIVE THERAPEUTIC STRATEGIES TO REDUCE OXIDATIVE STRESS

Oxidative stress in ageing and obesity

Ageing and obesity have a significant impact on global health,[37,38] which form a cohort high risk patient undergoing surgery. Whilst ageing is unavoidable, some of its biological consequences may be averted. The trajectory at which this occurs differs between individuals, and it is not the risk of ageing per se but the phenotypic expression of frailty that render patients at higher risk of perioperative complications.[39] Much still remains to be learnt from the underlying processes which drive ageing, it has been postulated that biological imperfectness, leading to cumulative damage over time, causes the overarching effect of this.[40] Harman’s free radical theory of ageing[41] forms an important piece of this puzzle, and a progressive weakening of our innate antioxidant system contributes to this.[42] One theory suggests the overlapping signalling pathways and positive feedback loops between OS and inflammation lead to a state of chronic inflammation (‘inflammageing’).[43] This renders cells more susceptible to injury, catabolism and age-related diseases,[3,44] involving progressive loss of muscle strength (sarcopenia) and increase in adiposity.[45] Obesity compounds the ageing process in some people and, in conjunction with metabolic syndrome, is another hotbed of OS.[46] Excessive deposition of adipose tissue acts as an endocrine organ, secreting cytokines and hormones, collectively termed adipokines. These adipokines trigger the release and activation of the innate immune systems, resulting in a state of increased inflammation and OS.[47] In addition, obese individuals are further prone to higher OS due to their lower antioxidant capacity, with demonstrated lower levels of SOD, CAT, and GPx as well as vitamins A, E and C concentrations.[48,49] Excessive fat accumulation also impairs glucose metabolism, and increases mitochondrial and peroxisomal oxidation, resulting in a vicious cycle of ROS production and cytokine release.[50]

Perioperative antioxidant use

Therapeutic strategies to reduce perioperative OS have the potential to improve clinical outcomes. Antioxidants prevent the transfer of electrons to and from molecular oxygen and organic molecules, accelerate ROS elimination and promote termination of ROS related reactions.[51] The evidence, however, for antioxidant use in chronic diseases has been conflicting.[52,53] In cancer, for example the most convincing evidence from epidemiological studies in the reduction of the incidence of carcinogenesis, have been from a diet rich in fruit and vegetables,[54,55] rather than the use of vitamin supplementation alone.

In the perioperative arena, vitamin C and N-acetylcysteine have shown some promising results post cardiac surgery; the use of vitamin C reduced postoperative atrial fibrillation [56] and N-acetylcysteine reduced the incidence of atrial fibrillation and acute kidney injury.[57] The therapeutic benefits of antioxidants in non-cardiac surgery remain uncertain and have generated discordant results,[32] a systematic review of the present literature in perioperative use of antioxidants in non-cardiac surgery is underway.[58]

Several promising agents are currently being investigated; some with intrinsic antioxidant capacities, such as curcumin and cannabidiol, others with pleiotropic effects in OS modulation, such as statins[59] and telmisartan.[60] To protect from IRI, anti-diabetics such as metformin can lead to a reduction in ROS formation during the reperfusion phase by inhibiting mitochondrial complex I.[61] Pioglitazone, a peroxisome proliferator activated receptor-γ (PPAR-γ) agonist (a nuclear receptor that interacts with multiple survivor genes) has been shown to regulate proteins involved in the tolerance to IRI.[62]

Resveratrol, a naturally occurring compound found in many plants including grapes, has pharmacological effects mimicking calorie restriction, exerting anti-inflammation and anti-OS properties.[63] Early work in animal models of sepsis have demonstrated ROS reduction and modulation of inflammation.[64] Melatonin could also potentially prove to be a strong candidate; it is an ancient molecule that has not altered in billions of years,[65] that is present in almost every organism on Earth[66] and has functionally diverse effects including anxiolysis, pain relief, delirium prevention, anti-inflammation and anti-oxidation.[67–69]

In this developing and complex field of redox medicine, it is important to highlight that the notion of perioperative antioxidant administration to ubiquitously reduce OS and improve outcomes is almost certainly over-simplistic. A more stratified approach involving multiple biomarkers and individual phenotyping may be required.[70] One tablet is highly unlikely to provide uniform benefit to every patient undergoing all types of surgery - a targeted approach focussing on the detection of OS-induced deficiencies, followed by supplementation tailored to individual patients could be an alternative approach.

Exercise: the panacea?

The WHO has identified physical inactivity as the 4th leading risk for global mortality, closely followed by obesity in 5th position.[71] The health benefits of regular exercise are widely accepted, particularly in obesity; exercise assists weight loss, reduces body fat percentage and increases lean body mass.[72] This has associated benefits in reducing metabolic disease, cardiovascular disease (CVD) and cancer.[73] However, 'fitness' *per se* may not necessarily be the key factor in this equation, it could simply be a surrogate measure of what is happening at the cellular level. Studies over the past 30 years have concentrated on the effects of ROS on skeletal and cardiac muscle.[74] ROS are released during exercise in a dose-dependent manner and directly interlinked to exercise-induced muscular modifications (fitness). The increase in oxygen demand must be matched by oxygen delivery and mitochondrial activity, and the latter is thought to drive the increased ROS production. Whilst the acute OS is likely to inflict some molecular damage, this is thought to be accompanied by an adaptive antioxidant response.[75] The balance of ROS release versus antioxidant response lies in the intensity and duration of exercise. The concept of hormesis, referring to a sub-lethal dose of toxin that can increase the tolerance of the organism to withstand higher doses of toxins, can be applied to exercise in this respect.[76] Acute strenuous activity has been linked to higher ROS release and a state of OS; however, moderate, sustained exercise conditioning induces the endogenous antioxidative system and provides protection against OS.[77] Studies on endurance exercise training and cardiac myocytes have demonstrated a phenotype which is resistant to IRI.[78] The induction of mitochondrial SOD in cardiac myocytes was required to achieve optimal cardio-protection.[79] Similar findings have been reflected in the skeletal muscle of individuals undergoing exercise training, they tend to have higher levels of antioxidants in their muscle.[80] Yet, supplementation with exogenous antioxidants during exercise training has yielded mixed results. Antioxidants may abrogate the health benefits of exercise training via interference with exercise-induced signaling pathways.[81] Exercise and antioxidant use in the ageing population, however, have indicated more promising results.[82]

The answer may fundamentally lie between the link between regular exercise and longevity.[41,83] There is mounting evidence that physical training and exercise combats the effects of ageing and reduces the effects of age-related diseases.[45] The effects of ageing and chronic illness can have deleterious effects in skeletal muscle functioning. Sarcopenia has been associated with chronic exposure to OS, inflammation and the reduction in antioxidant capacity as a result of aberrant cellular signalling.[75,84] Yet in contrast, elderly physically active individuals show antioxidant activity and lipid peroxidation levels similar to young sedentary subjects, emphasising the importance of regular physical activity to decelerate the age-associated impairment process. In perioperative medicine, prehabilitation has a growing body of work investigating the beneficial effects of exercise programmes prior to elective surgery.[85] Exercise in many instances have been shown to be more effective than costly pharmacological interventions.[86] This universal benefit aligns with the concept of exercise ‘training’ our cellular antioxidant systems; through mapping of the biological pathways involved, in order to prescribe individualised exercise programmes prior to surgery.

INTRAOPERATIVE OXIDATIVE DAMAGE LIMITATION: CAN ANYTHING BE DONE?

The effects of surgery

The intraoperative OS response to surgical intervention is heavily influenced by the magnitude of the surgery, the technique used, and the sequelae of inflammation and IRI experienced. Many studies have demonstrated increased OS levels following more invasive techniques compared to their minimally invasive counterparts. Demonstrated in open versus endovascular abdominal aortic aneurysm (AAA) repair [87], open versus laparoscopic abdominal surgeries,[88] and on-pump versus off-pump cardiopulmonary by-pass grafting (CABG).[89,90] There are some clinical associations linking postoperative recovery with levels of OS, however, the evidence base remains in its infancy. The length of IR in particular appears to be an important factor in the degree of OS. In a study of 132 patients who underwent one lung ventilation (OLV), the duration of OLV correlated with the degree of OS detected.[91] These effects can also be seen in orthopaedic surgery. The use of a tourniquet to provide a bloodless field has been associated with subsequent ROS release,[92] which correlated with localised tissue damage, delayed wound healing, and other postoperative complications relating to operative limb ischemia.[93]

An emerging theme arises from these studies, that is the wide range of small randomised controlled or observational trials using different OS markers collected from a variety of body fluids or tissues obtained from subjects, thus making overall evaluation challenging.

It should also be noted that not all forms of IR have deleterious effects on health. Indeed, some of the benefits have been harnessed in a technique known as ischemic preconditioning (IP). When multiple brief ischemic episodes to the coronary artery were delivered prior to a sustained occlusion in animal models, the infarct size was smaller in the preconditioned group compared to controls,[94] demonstrating that a brief period of ischemia protects an organ or tissue from subsequent more prolonged ischemia. Interestingly, the potential benefit from this phenomenon is not limited to the organ in question, there are systemic effects and this is referred to as remote IP. Commonly a limb receives a brief period of ischemia, in order to provide protection to distant vital organs.[95] Its clinical value has been explored in cardiac [96] and transplantation surgery[97] and it has been shown to reduce systemic OS in animal models of cardiac bypass[98] and cardiac arrest.[99].

The effects of anaesthesia

General anaesthesia

The modern anesthesiologist has a wide range of pharmaceutical agents at their disposal, however, virtually nothing is taught about their properties in relation to OS. The intravenous anaesthetic agent propofol has a phenolic structure similar to that of vitamin E, possibly accounting for its antioxidant properties.[100] In vitro and animal studies have demonstrated propofol to be a peroxynitrite scavenger, activator of heme oxygenase-1 and modulator protein kinase activity.[101,102] Conversely, ketamine has been shown to cause mitochondrial dysfunction and an increase in regional and global OS levels in the brain and liver.[103–105] The volatile anaesthetics are halogenated ethers and like propofol, they have also been shown to have properties that reduce OS. Most of our knowledge regarding this is from animal and cellular models where the use of isoflurane and sevoflurane have demonstrated antioxidant, anti-apoptotic and anti-inflammatory effects.[106,107] In particular, these two volatile agents have cardio-protective effects and, when used to precondition, can prevent damage from ischemia.[107,108] Associated renal and cerebral protective effects have also been demonstrated.[109] The antioxidant effect of total intravenous anesthesia (TIVA) has been compared to inhaled volatile anaesthetics in a small number of clinical studies. The decrease in OS markers with or without an increase in antioxidant capacity has been recorded in orthopaedic, thoracic, general surgical and hepatic surgeries where TIVA has been used.[110–114] Regional differences of OS release compared to systemic effects have been investigated in a limited number of thoracic surgical studies. The use of desflurane and propofol on alveolar inflammatory response from bronchial alveolar lavage (BAL) in the ventilated lung were examined after OLV. Patients in the propofol group demonstrated higher levels of granulocytes, TNF-alpha and sICAM.[115] Similarly, patients undergoing OLV demonstrated protective effects of sevoflurane compared to propofol, with lowered BAL fluid OS markers, a reduction in postoperative complications and ICU stay. This effect may be confounded by a longer length of OLV in the propofol group.[116] In addition, when localised effects of sevoflurane and desflurane were compared, MDA levels from BAL samples were higher in patients given desflurane.[117] The propensity for inducing higher OS by desflurane was also observed in two separate laparoscopic studies, where there was greater plasma lipid peroxidation in the desflurane group compared with sevoflurane; this effect was more pronounced when nitrous oxide (N_2O) was used.[117,118] Paradoxically, the OS pathway has been proposed as one of the ways in which volatile anaesthetic agents may pose a risk with long-term occupational exposure.[119] Furthermore, OS may be involved in neurotoxicity that general anaesthetic (GA) agents can cause in developing mammals,[120] in particular, repeated N_2O exposure has been demonstrated to cause OS-related neurotoxicity in rats;[121] the neurotoxic effects of repeated exposure of GA agents on the developing human brain is currently unknown and a pressing area for further research.[122] In summary, the heterogeneity of surgical techniques and mechanisms of action of anaesthetic agents, in conjunction with variations in patient factors, differences in OS biomarker selection and dissimilar clinical endpoints make assimilation of what evidence exists extremely challenging.

Regional anesthesia

A variety of techniques and pharmacological agents used in the delivery of regional anesthesia (RA) may have the potential to further modulate OS. RA, epidurals in particular, can provide superior pain control over opioid-based analgesia,[123,124] and pain is an important component of the neuro-humoral stress responses to surgery. Several small studies have detected an alteration in OS as a result of procedural pain in neonates,[125–127] the association of pain with OS have been demonstrated with simple pain stimuli such as a heel prick test. However, there is currently a dearth of data in perioperative pain responses and OS. In adults the majority of work has been conducted in patients with chronic pain, where chronic pain syndromes, including neuropathic pain have been linked to OS.[128,129] Whilst the use of rectus sheath blocks in abdominal cancer surgery did not demonstrate a change in OS markers,[130] epidural anesthesia for laparoscopic pelvic surgery did reduce MDA concentrations compared to GA.[131] This is clearly another area that would benefit from further investigation.

The role perioperative oxygen

Despite almost universal use perioperatively, there is ferocious debate around the ideal concentration of oxygen to use in order to ensure the best clinical outcomes.[132] The relevance of this is that ROS production is directly linked to cellular oxygen partial pressure.[133] In fact, both hypoxia and hyperoxia are associated with OS; whereas elaborate adaptive reactions are in place to cope with hypoxia this is not the case with hyperoxia, directly inflicting cell/tissue damage.[134] This debate was heightened after publication of the controversial World Healthcare Organisation (WHO) recommendations on perioperative measures to reduce surgical site infection. This document recommends that adult surgical patients undergoing GA with endotracheal intubation should receive an FIO_2 of 0.8 during and for up to six hours after surgery.[135] Curiously, this recommendation is supported by virtually no robust evidence.[136] In contrast, there is substantial evidence demonstrating that high oxygen concentrations cause damage to the lung parenchyma.[137] A retrospective study of intraoperative oxygen usage in more than 73,000 patients demonstrated a dose-dependent association to respiratory complications with higher 30-day mortality in the group receiving high FIO_2.[138] Follow-up analyses from one of the many perioperative ‘high versus low’ oxygen studies[139] has detected a number of concerning signals in patients given high (80%) versus low (30%) oxygen concentrations perioperatively; these are: i) increased long-term risk of myocardial infarction and other heart disease;[140] ii) increased long-term mortality;[141] and iii) reduced cancer-free survival.[142]

What we lack, is a clear understanding of the effects of hyperoxia on cellular function during surgery and the thresholds at which harm generally occurs. Given the reactive and toxic nature of oxygen, basic first principles would suggest that high concentration is only likely to be toxic and studies in the critically ill confirm this.[143–145] Very few studies have investigated the effects of oxygen concentration on OS production during surgery, and its causative links with clinical outcomes.

OXIDATIVE STRESS: RELEVANCE TO PERIOPERATIVE OUTCOME

The impact of preoperative risk factors and intraoperative propagation of OS tends to be borne out postoperatively and may manifest as unwanted complications and long-term harm. The biological mechanisms underlying the syndrome that leads to postoperative demise and multiple organ failure are poorly understood. Inflammation may well be a key element, and OS is likely to be an important contributor in this setting. Robust biomarkers of inflammation are now available to clinicians but those for OS are largely experimental. Whilst the synergistic rise in inflammatory markers and OS markers are well established, the clinical implications are not so well understood. A small but growing number of clinical studies have demonstrated a positive correlation of high perioperative OS with postoperative complications, these have been patients undergoing major surgery, including liver, lung resections and cardiac surgery.[4,34,91,146] The use of OS in predicting long-term outcomes may also be feasible; in a study of 21 cancer patients undergoing lung resection, lower values of diacron reactive oxygen metabolites (d-ROMs, a ROS measure of plasma or serum hydroperoxide levels using the Fenton reaction), were associated with a significantly higher 3 year survival. [35]

PERIOPERATIVE OXIDATIVE STRESS: LOOKING TO THE HORIZON

In the absence of a perioperative ‘silver bullet’, a multimodal approach to pragmatic OS reduction would seem sensible to improve clinical outcomes. Perhaps our strongest hand is to engage in public health messaging in order to reduce the OS burden in the general population, most of whom will require surgery at some point in their life. Smoking cessation, reduction in alcohol consumption, increased physical activity, a healthy diet and weight loss in obese individuals will improve the health of the nation (Figure 4). Some of these interventions can be implemented at the time a patient first knows that they will require surgery but will have far less impact in the short lead time between diagnosis and operation in a modern healthcare system. The population health approach may require anesthesiologists to stray even further from the operating room than we may be comfortable with, but if we are to improve global surgical outcomes this may ultimately be more effective than any drug we have to offer.

Opportunities are arising in the operating room, where as anesthesiologists we are able to personalise our approach to reduce postoperative complications. Through the careful selection of anaesthetic agents, techniques and appropriate titration of oxygen level, the term ‘balanced anesthesia’ should take a new meaning, moving away from clinicians’ choice based on experience, and towards robust physiological and biochemical measures. Select and targeted use of redox-active compounds (including and not exclusive to antioxidants), with tailored exercise programmes around the time of surgery may form part of a comprehensive package to minimise OS.

In time, we also need to develop robust methods of surgical risk stratification that include elements to identify those at particular risk to excessive OS. The use of an array of targeted biomarkers preoperatively may help to identify those with an underlying high OS burden. It is already known that frailty and pre-frailty are associated with raised systemic OS levels,[147] the potential for biological quantification of important risk factors is becoming a reality. However, in view of the complexity of redox biology and the multi-compartmental nature of the effects of OS across several levels of biological organisation, a systems-based, full body approach to reflect the redox state of the whole person should be what we strive for. Great advances have been made through genomic and transcriptomic technology; the study of metabolic alterations reflecting downstream changes using metabolomics should be adopted to study stress related biology. We should be moving away from static and single measures of OS readouts, towards dynamic measures of metabolites to characterise the changes during the perioperative period.[148]

CONCLUSION

Whilst our understanding of OS is growing, we need to focus attention to how it affects the patients we care for. Like inflammation, it is likely to play a major role in both healing and harm. As diagnostic biomarker techniques become more sophisticated, reliable and accessible, we need to weave this new information into more traditional models of care and re-think the way in which we select a particular technique or drug for the patient in front of us. Once we accept the paradox that oxygen is at the same time enabling life and one of our greatest enemies it will become easier to tackle the epidemic of OS by intervening in a more targeted fashion.

References

1. Martin D, McKenna H, Livina V. The human physiological impact of global deoxygenation. *J Physiol Sci*. 2017;67(1):97-106. doi:10.1007/s12576-016-0501-0
2. Frijhoff J, Winyard PG, Zarkovic N, et al. Clinical Relevance of Biomarkers of Oxidative Stress. *Antioxid Redox Signal*. 2015;23(14):1144-1170. doi:10.1089/ars.2015.6317
3. López-Armada MJ, Riveiro-Naveira RR, Vaamonde-García C, Valcárcel-Ares MN. Mitochondrial dysfunction and the inflammatory response. *Mitochondrion*. 2013;13(2):106-118. doi:10.1016/J.MITO.2013.01.003
4. Senoner T, Schindler S, Stättner S, Öfner D, Troppmair J, Primavesi F. Associations of Oxidative Stress and Postoperative Outcome in Liver Surgery with an Outlook to Future Potential Therapeutic Options. *Oxid Med Cell Longev*. 2019;2019:1-18. doi:10.1155/2019/3950818
5. Walker JE, Collinson IR, Van Raaij MJ, Runswick MJ. [11] Structural analysis of ATP synthase from bovine heart mitochondria. In: *Mitochondrial Biogenesis and Genetics Part A*. Vol 260. Academic Press; 1995:163-190. doi:10.1016/0076-6879(95)60136-8
6. Brand MD. The sites and topology of mitochondrial superoxide production. *Exp Gerontol*. 2010;45(7-8):466-472. doi:10.1016/j.exger.2010.01.003
7. Di Meo S, Reed TT, Venditti P, Victor VM. Role of ROS and RNS Sources in Physiological and Pathological Conditions. *Oxid Med Cell Longev*. 2016;2016:1245049. doi:10.1155/2016/1245049

8. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. *Curr Biol*. 2014;24(10):R453-62. doi:10.1016/j.cub.2014.03.034

9. Sies H, Berndt C, Jones DP. Oxidative Stress. *Annu Rev Biochem*. 2017;86(1):715-748. doi:10.1146/annurev-biochem-061516-045037

10. Nimse SB, Pal D. Free radicals, natural antioxidants, and their reaction mechanisms. *RSC Adv*. 2015;5(35):27986-28006. doi:10.1039/C4RA13315C

11. Hernández-Camacho JD, Bernier M, López-Lluch G, Navas P. Coenzyme Q10 Supplementation in Aging and Disease. *Front Physiol*. 2018;9:44. doi:10.3389/fphys.2018.00044

12. Kohen R, Nyska A. Invited Review: Oxidation of Biological Systems: Oxidative Stress Phenomena, Antioxidants, Redox Reactions, and Methods for Their Quantification. *Toxicol Pathol*. 2002;30(6):620-650. doi:10.1080/01926230290166724

13. Ademowo OS, Dias HKI, Burton DGA, Griffiths HR. Lipid (per) oxidation in mitochondria: an emerging target in the ageing process? *Biogerontology*. 2017;18(6):859-879. doi:10.1007/s10522-017-9710-z

14. Anderson EJ, Katunga LA, Willis MS. Mitochondria as a source and target of lipid peroxidation products in healthy and diseased heart. *Clin Exp Pharmacol Physiol*. 2012;39(2):179-193. doi:10.1111/j.1440-1681.2011.05641.x

15. Patinen T, Adinolfi S, Cortés CC, Härkönen J, Jawahar Deen A, Levonen A-L. Regulation of stress signaling pathways by protein lipoxidation. *Redox Biol*. January 2019:101114. doi:10.1016/J.REDOX.2019.101114

16. Zhang J, Wang X, Vikash V, et al. ROS and ROS-Mediated Cellular Signaling. *Oxid Med Cell Longev*. 2016;2016:1-18. doi:10.1155/2016/4350965

17. Jones DP, Sies H. The Redox Code. *Antioxid Redox Signal*. 2015;23(9):734-746. doi:10.1089/ars.2015.6247

18. Radi R. Oxygen radicals, nitric oxide, and peroxynitrite: Redox pathways in molecular medicine. *Proc Natl Acad Sci U S A*. 2018;115(23):5839-5848. doi:10.1073/pnas.1804932115

19. Giles, G and Jacobs C. Review Reactive Sulfur Species: An Emerging Concept in Oxidative Stress. *Biol Chem*. 2002;383:375-388. doi:https://doi.org/10.1515/BC.2002.042

20. Fukuto JM, Ignarro LJ, Nagy P, et al. Biological hydropersulfides and related polysulfides - a new concept and perspective in redox biology. *FEBS Lett*. 2018;592(12):2140-2152. doi:10.1002/1873-3468.13090

21. Cortese-Krott MM, Koning A, Kuhnle GGC, et al. The Reactive Species Interactome: Evolutionary Emergence, Biological Significance, and Opportunities for Redox Metabolomics and Personalized Medicine. *Antioxid Redox Signal*. 2017;27(10):684-712. doi:10.1089/ars.2017.7083

22. Yue L, Yao H. Mitochondrial dysfunction in inflammatory responses and cellular senescence: pathogenesis and pharmacological targets for chronic lung diseases. *Br J Pharmacol*. 2016;173(15):2305-2318. doi:10.1111/bph.13518

23. Desborough JP. The stress response to trauma and surgery. *BJA Br J Anaesth*. 2000;85(1):109-117. doi:10.1093/bja/85.1.109

24. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery*. 2000;127(2):117-126. doi:10.1067/MSY.2000.101584

25. Naik E, Dixit VM. Mitochondrial reactive oxygen species drive proinflammatory cytokine production. *J Exp Med*. 2011;208(3):417-420. doi:10.1084/jem.20110367

26. Zhao H, Kilgas S, Alam A, Eguchi S, Ma D. The role of extracellular adenosine triphosphate in ischemic organ injury. *Crit Care Med*. 2016;44(5):1000-1012. doi:10.1097/CCM.0000000000001603

27. Kalogeris T, Bao Y, Korthuis RJ. Mitochondrial reactive oxygen species: a double edged sword in ischemia/reperfusion vs preconditioning. *Redox Biol*. 2014;2:702-714. doi:10.1016/j.redox.2014.05.006

28. Wu LL, Chiou C-C, Chang P-Y, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. doi:10.1016/j.cccn.2003.09.010

29. Soysal P, Isik AT, Carvalho AF, et al. Oxidative stress and frailty: A systematic review and synthesis of the best evidence. *Maturitas*. 2017;99:66-72. doi:10.1016/j.maturitas.2017.01.006

30. Woolley JF, Stanicka J, Cotter TG. Recent advances in reactive oxygen species measurement in biological systems. *Trends Biochem Sci*. 2013;38(11):556-565. doi:10.1016/j.tibs.2013.08.009

31. Griendling KK, Touyz RM, Zweier JL, et al. Measurement of Reactive Oxygen Species, Reactive Nitrogen Species, and Redox-Dependent Signaling in the Cardiovascular System: A Scientific Statement From the American Heart Association. *Circ Res*. 2016;119(5):e39-75.

doi:10.1161/RES.0000000000000110

32. Egea J, Fabregat I, Frapart YM, et al. European contribution to the study of ROS_ A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS). 2017. doi:10.1016/j.redox.2017.05.007

33. Mizuno Y, Iwata H, Yamamoto H, et al. Influence of smoking on perioperative oxidative stress after pulmonary resection. *Surg Today*. 2016;46(2):183-187. doi:10.1007/s00595-015-1132-4

34. Schwarz C, Fitschek F, Bar-Or D, et al. Inflammatory response and oxidative stress during liver resection. Strnad P, ed. *PLoS One*. 2017;12(10):e0185685. doi:10.1371/journal.pone.0185685

35. Araki O, Matsumura Y, Inoue T, et al. Association of Perioperative Redox Balance on Long-Term Outcome in Patients Undergoing Lung Resection. *Ann Thorac Cardiovasc Surg*. 2018;24(1):13-18. doi:10.5761/atcs.oa.17-00127

36. Rosenfeldt F, Wilson M, Lee G, et al. Oxidative stress in surgery in an ageing population: Pathophysiology and therapy. *Exp Gerontol*. 2013;48(1):45-54. doi:10.1016/j.exger.2012.03.010

37. *World Population Prospects The 2017 Revision*. https://esa.un.org/unpd/wpp/Publications/Files/WPP2017_KeyFindings.pdf. Accessed November 28, 2018.

38. Meldrum DR, Morris MA, Gambone JC. Obesity pandemic: causes, consequences, and solutions—but do we have the will? *Fertil Steril*. 2017;107(4):833-839. doi:10.1016/J.FERTNSTERT.2017.02.104

39. Wu I-C, Lin C-C, Hsiung CA. Emerging roles of frailty and inflammaging

in risk assessment of age-related chronic diseases in older adults: the intersection between aging biology and personalized medicine. *BioMedicine*. 2015;5(1):1. doi:10.7603/s40681-015-0001-1

40. Gladyshev VN. The free radical theory of aging is dead. Long live the damage theory! *Antioxid Redox Signal*. 2014;20(4):727-731. doi:10.1089/ars.2013.5228

41. Harman D. Aging: A Theory Based on Free Radical and Radiation Chemistry. *J Gerontol*. 1956;11(3):298-300. doi:10.1093/geronj/11.3.298

42. Chung HY, Cesari M, Anton S, et al. Molecular inflammation: underpinnings of aging and age-related diseases. *Ageing Res Rev*. 2009;8(1):18-30. doi:10.1016/j.arr.2008.07.002

43. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E D, G. B. Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *Ann N Y Acad Sci*. 2006;908(1):244-254. doi:10.1111/j.1749-6632.2000.tb06651.x

44. Loeser RF. Review Aging and osteoarthritis: the role of chondrocyte senescence and aging changes in the cartilage matrix. *Osteoarthr Cartil*. 17:971-979. doi:10.1016/j.joca.2009.03.002

45. Sallam N, Laher I. Exercise Modulates Oxidative Stress and Inflammation in Aging and Cardiovascular Diseases. *Oxid Med Cell Longev*. 2016;2016:7239639. doi:10.1155/2016/7239639

46. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004;114(12):1752-1761. doi:10.1172/JCI21625

47. Fonseca-Alaniz MH, Takada J, Alonso-Vale MIC, Lima FB. Adipose tissue as an endocrine organ: from theory to practice. *J Pediatr (Rio J)*. 2007;0(0). doi:10.2223/JPED.1709

48. Amirkhizi, F, Siassi, F, Minaie, S, Djalali, M, Rahimi, A, Chamari M. . *ARYA Atheroscler*. 2005;2(4).

49. Ozata M, Mergen M, Oktenli C, et al. Increased oxidative stress and hypozincemia in male obesity. *Clin Biochem*. 2002;35(8):627-631. doi:10.1016/S0009-9120(02)00363-6

50. Marseglia L, Manti S, D’Angelo G, et al. Oxidative stress in obesity: a critical component in human diseases. *Int J Mol Sci*. 2014;16(1):378-400. doi:10.3390/ijms16010378

51. Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*. 5th ed. Oxford University Press; 2015.

52. Mayne ST. Oxidative Stress, Dietary Antioxidant Supplements, and Health: Is the Glass Half Full or Half Empty? *Cancer Epidemiol Biomarkers Prev*. 2013;22(12):2145-2147. doi:10.1158/1055-9965.EPI-13-1026

53. Willcox JK, Ash SL, Catignani GL. Antioxidants and Prevention of Chronic Disease. *Crit Rev Food Sci Nutr*. 2004;44(4):275-295. doi:10.1080/10408690490468489

54. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. *Nutr Cancer*. 1992;18(1):1-29. doi:10.1080/01635589209514201

55. Howe GR, Hirohata T, Hislop TG, et al. Dietary Factors and Risk of Breast Cancer: Combined Analysis of 12 Case--Control Studies. *JNCI J*

Natl Cancer Inst. 1990;82(7):561-569. doi:10.1093/jnci/82.7.561

56. Geng J, Qian J, Si W, Cheng H, Ji F, Shen Z. The clinical benefits of perioperative antioxidant vitamin therapy in patients undergoing cardiac surgery: a meta-analysis. *Interact Cardiovasc Thorac Surg*. 2017;236:814-822. doi:10.1093/icvts/ivx178
57. Ali-Hassan-Sayegh S, Mirhosseini SJ, Tahernejad M, et al. Impact of antioxidant supplementations on cardio-renal protection in cardiac surgery: an updated and comprehensive meta-analysis and systematic review. *Cardiovasc Ther*. 2016;34(5):360-370. doi:10.1111/1755-5922.12207
58. Stevens JL, McKenna H, Gurusamy KS, et al. Perioperative antioxidants for adults undergoing elective non-cardiac surgery. *Cochrane Database Syst Rev*. 2018;(11). doi:10.1002/14651858.CD013174
59. Liu A, Wu Q, Guo J, et al. Statins: Adverse reactions, oxidative stress and metabolic interactions. *Pharmacol Ther*. October 2018. doi:10.1016/J.PHARMTHERA.2018.10.004
60. Nakano A, Hattori Y, Aoki C, Jojima T, Kasai K. Telmisartan inhibits cytokine-induced nuclear factor-κB activation independently of the peroxisome proliferator-activated receptor-γ. *Hypertens Res*. 2009;32(9):765-769. doi:10.1038/hr.2009.95
61. Bridges HR, Jones AJY, Pollak MN, Hirst J. Effects of metformin and other biguanides on oxidative phosphorylation in mitochondria. *Biochem J*. 2014;462(3):475-487. doi:10.1042/BJ20140620
62. Rodríguez-Lara SQ, Cardona-Muñoz EG, Ramírez-Lizardo EJ, et al.

Alternative Interventions to Prevent Oxidative Damage following Ischemia/Reperfusion. *Oxid Med Cell Longev*. 2016;2016:1-16. doi:10.1155/2016/7190943

63. Chung JH, Manganiello V, Dyck JRB. Resveratrol as a calorie restriction mimetic: therapeutic implications. *Trends Cell Biol*. 2012;22(10):546-554. doi:10.1016/j.tcb.2012.07.004
64. Wang X, Buechler NL, Yoza BK, McCall CE, Vachharajani VT. Resveratrol attenuates microvascular inflammation in sepsis via SIRT-1-Induced modulation of adhesion molecules in ob/ob mice. *Obesity (Silver Spring)*. 2015;23(6):1209-1217. doi:10.1002/oby.21086
65. Manchester LC, Coto-Montes A, Boga JA, et al. Melatonin: an ancient molecule that makes oxygen metabolically tolerable. *J Pineal Res*. 2015;59(4):403-419. doi:10.1111/jpi.12267
66. Reiter RJ, Rosales-Corral S, Tan DX, Jou MJ, Galano A, Xu B. Melatonin as a mitochondria-targeted antioxidant: one of evolution’s best ideas. *Cell Mol Life Sci*. 2017;74(21):3863-3881. doi:10.1007/s00018-017-2609-7
67. Samarkandi A, Naguib M, Riad W, et al. Melatonin vs. midazolam premedication in children: a double-blind, placebo-controlled study. *Eur J Anaesthesiol*. 2005;22(3):189-196. doi:10.1017/S0265021505000335
68. Mowafi HA, Ismail SA. Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anesthesia. *Anesth Analg*. 2008;107(4):1422-1426. doi:10.1213/ane.0b013e318181f689
69. Reiter RJ, Mayo JC, Tan D-X, Sainz RM, Alatorre-Jimenez M, Qin L.

Melatonin as an antioxidant: under promises but over delivers. *J Pineal Res*. 2016;61(3):253-278. doi:10.1111/jpi.12360

70. Mayne ST, Ferrucci LM, Cartmel B. Lessons Learned from Randomized Clinical Trials of Micronutrient Supplementation for Cancer Prevention. *Annu Rev Nutr*. 2012;32(1):369-390. doi:10.1146/annurev-nutr-071811-150659
71. *WHO. Global Health Risks. Mortality and Burden of Disease Attributable to Selected Major Risks*. Geneva; 2009.
72. Willis LH, Slentz CA, Bateman LA, et al. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J Appl Physiol*. 2012;113(12):1831-1837. doi:10.1152/japplphysiol.01370.2011
73. McQueen MA. Exercise aspects of obesity treatment. *Ochsner J*. 2009;9(3):140-143.
74. Powers SK, Radak Z, Ji LL. Exercise-induced oxidative stress: past, present and future. *J Physiol*. 2016;594(18):5081-5092. doi:10.1113/JP270646
75. Steinbacher P, Eckl P. Impact of oxidative stress on exercising skeletal muscle. *Biomolecules*. 2015;5(2):356-377. doi:10.3390/biom5020356
76. Ji L. Exercise-induced Modulation of Antioxidant Defense. *Ann N Y Acad Sci*. 2002;959(1):82-92. doi:10.1111/j.1749-6632.2002.tb02085.x
77. Atalay M, Laaksonen DE. Diabetes, oxidative stress and physical exercise. *J Sports Sci Med*. 2002;1(1):1-14.
78. Powers SK, Hogan MC. Exercise and oxidative stress. *J Physiol*. 2016;594(18):5079-5080. doi:10.1113/JP272255

79. Yamashita N, Hoshida S, Otsu K, Asahi M, Kuzuya T, Hori M. Exercise provides direct biphasic cardioprotection via manganese superoxide dismutase activation. *J Exp Med*. 1999;189(11):1699-1706.

80. Sen CK. Oxidants and antioxidants in exercise. *J Appl Physiol*. 1995;79(3):675-686. doi:10.1152/jappl.1995.79.3.675

81. Merry TL, Ristow M. Do antioxidant supplements interfere with skeletal muscle adaptation to exercise training? *J Physiol*. 2016;594(18):5135-5147. doi:10.1113/JP270654

82. Simioni C, Zauli G, Martelli AM, et al. Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging. *Oncotarget*. 2018;9(24):17181-17198. doi:10.18632/oncotarget.24729

83. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature*. 2000;408(6809):239-247. doi:10.1038/35041687

84. Moylan JS, Reid MB. Oxidative stress, chronic disease, and muscle wasting. *Muscle Nerve*. 2007;35(4):411-429. doi:10.1002/mus.20743

85. Carli F, Gillis C, Scheede-Bergdahl C. Promoting a culture of prehabilitation for the surgical cancer patient. *Acta Oncol (Madr)*. 2017;56(2):128-133. doi:10.1080/0284186X.2016.1266081

86. Pedersen BK. The Physiology of Optimizing Health with a Focus on Exercise as Medicine. *Annu Rev Physiol*. 2019;81(1):607-627. doi:10.1146/annurev-physiol-020518-114339

87. Aivatidi C, Vourliotakis G, Georgopoulos S, Sigala F, Bastounis E PE. Oxidative stress during abdominal aortic aneurysm repair – Biomarkers and antioxidant’s protective effect: a review. *Eur Rec Med Pharmacol Sci*. 2011;15(3):245-252.

88. Arsalani-Zadeh R, Ullah S, Khan S, Macfie J. Oxidative Stress in Laparoscopic Versus Open Abdominal Surgery: A Systematic Review. *J Surg Res*. 2011;169(1):e59-e68. doi:10.1016/j.jss.2011.01.038

89. Biglioli P. Biological effects of off-pump vs. on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. *Eur J Cardio-Thoracic Surg*. 2003;24(2):260-269. doi:10.1016/S1010-7940(03)00295-1

90. Gerritsen WBM, Boven WJP Van, Driessen AHG, Haas FJLM, Aarts LPHJ. Off-pump versus on-pump coronary artery bypass grafting : oxidative stress and renal function q. *Eur J Cardio-thoracic Surg 20*. 2001;20:923-929.

91. Misthos P, Katsaragakis S, Theodorou D, Milingos N, Skottis I. The degree of oxidative stress is associated with major adverse effects after lung resection: A prospective study. 2006. doi:10.1016/j.ejcts.2005.12.027

92. Cheng Y-J, Chien C-T, Chen C-F. Oxidative stress in bilateral total knee replacement, under ischaemic tourniquet. *J Bone &amp; Jt Surgery, Br Vol*. 2003;85-B(5):679 LP - 682. http://www.bjj.boneandjoint.org.uk/content/85-B/5/679.abstract.

93. Smith TO, Hing CB. Is a tourniquet beneficial in total knee replacement surgery? *Knee*. 2018;17(2):141-147. doi:10.1016/j.knee.2009.06.007

94. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74(5). doi:10.1161/01.CIR.74.5.1124

95. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning:

underlying mechanisms and clinical application. *Cardiovasc Res*. 2008;79(3):377-386. doi:10.1093/cvr/cvn114

96. Hausenloy DJ, Mwamure PK, Venugopal V, et al. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet (London, England)*. 2007;370(9587):575-579. doi:10.1016/S0140-6736(07)61296-3

97. Farooqui W, Pommergaard HC, Rasmussen A. Remote ischemic preconditioning of transplant recipients to reduce graft ischemia and reperfusion injuries: A systematic review. *Transplant Rev*. 2018;32(1):10-15. doi:10.1016/J.TRRE.2017.06.001

98. Arvola O, Haapanen H, Herajärvi J, et al. Remote Ischemic Preconditioning Attenuates Oxidative Stress during Cardiopulmonary Bypass. *Heart Surg Forum*. 2016;19(4):192. doi:10.1532/hsf.1590

99. Arvola O, Haapanen H, Herajärvi J, et al. Remote Ischemic Preconditioning Reduces Cerebral Oxidative Stress Following Hypothermic Circulatory Arrest in a Porcine Model. *Semin Thorac Cardiovasc Surg*. 2016;28(1):92-102. doi:10.1053/J.SEMTCVS.2016.01.005

100. Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG. The antioxidant potential of propofol (2,6- diisopropylphenol). *Br J Anaesth*. 1992;68:613-618. doi:10.1093/bja/68.6.613

101. Kahraman S. Propofol Is a Peroxynitrite Scavenger. *Anesth Analg*. 1997;84(5):1127-1129.

102. Vasileiou I, Xanthos T, Koudouna E, et al. Propofol: A review of its non-

anaesthetic effects. *Eur J Pharmacol*. 2009;605:1-8. doi:10.1016/j.ejphar.2009.01.007

103. de Oliveira L, dos S. Spiazzi CM, Bortolin T, et al. Different sub-anesthetic doses of ketamine increase oxidative stress in the brain of rats. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2009;33(6):1003-1008. doi:10.1016/J.PNPBP.2009.05.010
104. Venâncio C, Félix L, Almeida V, et al. Acute Ketamine Impairs Mitochondrial Function and Promotes Superoxide Dismutase Activity in the Rat Brain. *Anesth Analg*. 2015;120(2):320-328. doi:10.1213/ANE.0000000000000539
105. Kalkan Y, Tomak Y, Altuner D, et al. Hepatic effects of ketamine administration for 2 weeks in rats. doi:10.1177/0960327112472990
106. Bedirli N, Bagriacik EU, Emmez H, Yilmaz G, Unal Y, Ozkose Z. Sevoflurane and Isoflurane Preconditioning Provides Neuroprotection by Inhibition of Apoptosis-related mRNA Expression in a Rat Model of Focal Cerebral Ischemia. *J Neurosurg Anesthesiol*. 2012;24(4):336-344. doi:10.1097/ANA.0b013e318266791e
107. Jamnicki-abegg M, Weihrauch D, Ph D, Pagel PS, Ph D. Isoflurane Inhibits Cardiac Myocyte Apoptosis during Oxidative and Inflammatory Stress by Activating Akt and Enhancing Bcl-2 Expression. 2018;(5):1006-1014.
108. Kunst G, Klein AA. Peri-operative anaesthetic myocardial preconditioning and protection – cellular mechanisms and clinical relevance in cardiac anaesthesia. doi:10.1111/anae.12975
109. Erturk E. Ischemia-reperfusion injury and volatile anesthetics. *Biomed*

Res Int. 2014;2014:526301. doi:10.1155/2014/526301

110. Halladin NL, Zahle F V., Rosenberg J, Gögenur I. Interventions to reduce tourniquet-related ischaemic damage in orthopaedic surgery: a qualitative systematic review of randomised trials. *Anaesthesia*. 2014;69(9):1033-1050. doi:10.1111/anae.12664

111. Erturk E, Topaloglu S, Dohman D, et al. The comparison of the effects of sevoflurane inhalation anesthesia and intravenous propofol anesthesia on oxidative stress in one lung ventilation. *Biomed Res Int*. 2014;2014:360936. doi:10.1155/2014/360936

112. Huang C-H, Wang Y-P, Wu P-Y, Chien C-T, Cheng Y-J. Propofol infusion shortens and attenuates oxidative stress during one lung ventilation. *Acta Anaesthesiol Taiwan*. 2008;46(4):160-165. doi:10.1016/S1875-4597(09)60003-5

113. De La Cruz JP, Zanca A, Carmona JA, de la Cuesta FS. The effect of propofol on oxidative stress in platelets from surgical patients. *Anesth Analg*. 1999;89(4):1050-1055.

114. Ge M, Chen H, Zhu Q, et al. Propofol post-conditioning alleviates hepatic ischaemia reperfusion injury via BRG1-mediated Nrf2/HO-1 transcriptional activation in human and mice. *J Cell Mol Med*. 2017;21(12):3693-3704. doi:10.1111/jcmm.13279

115. Schilling T, Kozian A, Kretzschmar M, et al. Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation. *Br J Anaesth*. 2007;99(3):368-375. doi:10.1093/bja/aem184

116. Conno E De, Steurer MP, Wittlinger M, Zalunardo MP. Anesthetic-

induced Improvement of the Inflammatory Response to One-lung Ventilation. 2018;(6):1316-1326.

117. Koksal GM, Sayilgan C, Aydin S, Uzun H, Oz H. The effects of sevoflurane and desflurane on lipid peroxidation during laparoscopic cholecystectomy. *Eur J Anaesthesiol*. 2004;21(3):217-220. doi:10.1017/S0265021504003102

118. Sivaci R, Kahraman A, Serteser M, Sahin DA, Dilek ON. Cytotoxic effects of volatile anesthetics with free radicals undergoing laparoscopic surgery. 2006. doi:10.1016/j.clinbiochem.2006.01.001

119. Türkan H, Aydin A, Sayal A. Effect of Volatile Anesthetics on Oxidative Stress Due to Occupational Exposure. *World J Surg*. 2005;29(4):540-542. doi:10.1007/s00268-004-7658-z

120. Kovacic P, Somanathan R. Mechanism of Anesthetic Toxicity: Metabolism, Reactive Oxygen Species, Oxidative Stress, and Electron Transfer. *ISRN Anesthesiol*. 2011;2011:1-10. doi:10.5402/2011/402906

121. Singh SK, Misra UK, Kalita J, Bora HK, Murthy RC. Nitrous oxide related behavioral and histopathological changes may be related to oxidative stress. *Neurotoxicology*. 2015;48:44-49. doi:10.1016/J.NEURO.2015.03.003

122. Andropoulos DB. Effect of Anesthesia on the Developing Brain: Infant and Fetus. *Fetal Diagn Ther*. 2018;43(1):1-11. doi:10.1159/000475928

123. Werawatganon T, Charuluxananan S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. In: Werawatganon T, ed. *The Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons,

Ltd; 2005. doi:10.1002/14651858.CD004088.pub2

124. Nishimori M, Ballantyne JC, Low JH. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. In: Nishimori M, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2006. doi:10.1002/14651858.CD005059.pub2

125. Slater L, Asmerom Y, Boskovic DS, et al. Procedural pain and oxidative stress in premature neonates. *J Pain*. 2012;13(6):590-597. doi:10.1016/j.jpain.2012.03.010

126. Perrone S, Bellieni C V., Negro S, et al. Oxidative Stress as a Physiological Pain Response in Full-Term Newborns. *Oxid Med Cell Longev*. 2017;2017:1-7. doi:10.1155/2017/3759287

127. Bellieni C V., Iantorno L, Perrone S, et al. Even routine painful procedures can be harmful for the newborn. *Pain*. 2009;147(1):128-131. doi:10.1016/j.pain.2009.08.025

128. Kolberg C, Horst A, Moraes MS, et al. Peripheral Oxidative Stress Blood Markers in Patients With Chronic Back or Neck Pain Treated With High-Velocity, Low-Amplitude Manipulation. *J Manipulative Physiol Ther*. 2015;38(2):119-129. doi:10.1016/J.JMPT.2014.11.003

129. Carrasco C, Naziroğlu M, Rodríguez AB, Pariente JA. Neuropathic Pain: Delving into the Oxidative Origin and the Possible Implication of Transient Receptor Potential Channels. *Front Physiol*. 2018;9. doi:10.3389/FPHYS.2018.00095

130. Purdy M, Kärkkäinen J, Kokki M, et al. Does Rectus Sheath Block Analgesia Alter Levels of the Oxidative Stress Biomarker Glutathione

Peroxidase: A Randomised Trial of Patients with Cancer and Benign Disease. *Anticancer Res*. 2017;37(2):897-902. doi:10.21873/anticanres.11396

131. Shin S, Bai SJ, Rha KH, So Y, Oh YJ. The effects of combined epidural and general anesthesia on the autonomic nervous system and bioavailability of nitric oxide in patients undergoing laparoscopic pelvic surgery. *Surg Endosc*. 2013;27(3):918-926. doi:10.1007/s00464-012-2536-5
132. Martin DS, Grocott MPW. Oxygen therapy and anaesthesia: too much of a good thing? *Anaesthesia*. 2015;70(5):522-527. doi:10.1111/anae.13081
133. Clanton TL, Hogan MC, Gladden LB. Regulation of Cellular Gas Exchange, Oxygen Sensing, and Metabolic Control. In: *Comprehensive Physiology*. Vol 3. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2013:1135-1190. doi:10.1002/cphy.c120030
134. Mantell L, Chandel NS, Scott Budinger GR. Serial Review: Redox Signaling in Immune Function and Cellular Responses in Lung Injury and Diseases Serial Review Editors: Victor Darley-Usmar The cellular basis for diverse responses to oxygen ☆. 2006. doi:10.1016/j.freeradbiomed.2006.10.048
135. Allegranzi B, Bischoff P, de Jonge S, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis*. 2016;16(12):e276-e287. doi:10.1016/S1473-3099(16)30398-X
136. Myles PS, Kurz A. Supplemental oxygen and surgical site infection:

getting to the truth. *Br J Anaesth*. 2017;119(1):13-15. doi:10.1093/bja/aex096

137. Kallet RH, Matthay MA. Hyperoxic acute lung injury. *Respir Care*. 2013;58(1):123-141. doi:10.4187/respcare.01963

138. Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, et al. High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. *Br J Anaesth*. 2017;119(1):140-149. doi:10.1093/bja/aex128

139. Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of High Perioperative Oxygen Fraction on Surgical Site Infection and Pulmonary Complications After Abdominal Surgery. *JAMA*. 2009;302(14):1543. doi:10.1001/jama.2009.1452

140. Fonnes S, Gögenur I, Søndergaard ES, et al. Perioperative hyperoxia - Long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial. *Int J Cardiol*. 2016;215:238-243. doi:10.1016/j.ijcard.2016.04.104

141. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS, Group PT. Anesthesia Patient Safety Foundation Increased Long-Term Mortality After a High Perioperative Inspiratory Oxygen Fraction During Abdominal Surgery: Follow-Up of a Randomized Clinical Trial. doi:10.1213/ANE.0b013e3182652a51

142. Meyhoff CS, Jorgensen LN, Wetterslev J, Siersma VD, Rasmussen LS. Risk of new or recurrent cancer after a high perioperative inspiratory oxygen fraction during abdominal surgery. *Br J Anaesth*. 2014;113:i74-i81. doi:10.1093/bja/aeu110

143. Girardis M, Busani S, Damiani E, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit. *JAMA*. 2016;316(15):1583. doi:10.1001/jama.2016.11993

144. Helmerhorst HJF, Arts DL, Schultz MJ, et al. Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care*. *Crit Care Med*. 2017;45(2):187-195. doi:10.1097/CCM.0000000000002084

145. Ruggiu M, Aissaoui N, Nael J, et al. Hyperoxia effects on intensive care unit mortality: a retrospective pragmatic cohort study. *Crit Care*. 2018;22(1):218. doi:10.1186/s13054-018-2142-6

146. Billings Iv FT, Pretorius M, Schildcrout JS, et al. Obesity and Oxidative Stress Predict AKI after Cardiac Surgery CLINICAL EPIDEMIOLOGY. *J Am Soc Nephrol*. 2012;23:1221-1228. doi:10.1681/ASN.2011090940

147. Soysal P, Isik AT, Carvalho AF, et al. Oxidative stress and frailty: A systematic review and synthesis of the best evidence. *Maturitas*. 2017;99:66-72. doi:10.1016/J.MATURITAS.2017.01.006

148. Santolini J, Wootton SA, Jackson AA, Feelisch M. The Redox architecture of physiological function. *Curr Opin Physiol*. 2019;9:34-47. doi:10.1016/J.COPHYS.2019.04.009

149. Dada LA, Sznajder JI. Mitochondrial Ca^2+ and ROS take center stage to orchestrate TNF-α-mediated inflammatory responses. *J Clin Invest*. 2011;121(5):1683-1685. doi:10.1172/JCI57748

150. Kujoth GC, Hiona A, Pugh TD, et al. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science*. 2005;309(5733):481-484. doi:10.1126/science.1112125

Figure legends

Fig 1. Mitochondrial and extra-mitochondrial sources of ROS

The extra mitochondrial sources include peroxisomes, lysosomes, the endoplasmic reticulum, the plasma membrane and cytosolic proteins and small molecules.

Fig 2. The process of ROS production

Enzymatic release of superoxide ($O_2\cdot^-$) can originate from activities of xanthine oxidase (XO), NAPH oxidase (NOX) and respiratory complexes within the mitochondrial electron transport chain (ECT). Under some conditions, nitric oxide synthase (NOS) can produce both $O_2\cdot^-$ and nitric oxide (NO) to immediately react and form the potent pro-oxidant peroxynitrite ($ONOO^-$). Superoxide dismutase (SOD) converts $O_2\cdot^-$ into hydrogen peroxide (H_2O_2). In addition to inactivation by catalase, H_2O_2 reacts with glutathione peroxidase (GPX) and reduced glutathione (GSH) to form water (H_2O) and glutathione disulfide (GSSG). Additional enzymes involved in this process include peroxiredoxins and thioredoxins. Myeloperoxidase (MPO) produces hypochlorite (HOCl) from the reaction of H_2O_2 with chloride anions (Cl^-), the Fenton reaction is a non-enzymatic process involving ferrous (Fe^{2+}) ions and H_2O_2 to produce to the highly reactive hydroxl radical ($OH_\cdot$).

Fig 3. A proposed model for the relationship between mitochondrial dysfunction and inflammation

An adapted diagram from Lopez-Armada and colleagues, 2013.[3] During the initial innate immune response ROS is generated from ROS secreting organelles within leukocytes. This leads to activation of downstream redox-sensitive transcription factors, such as nuclear factor-κB (NF-κB), and cytokines, chemokines and iNOS in cells of the surrounding tissue.[42] In the acute phase, changes to mitochondrial enzyme activities cause increases in calcium influx, mitochondrial dysfunction and cell death.[149] This in turn results in the release of DAMPs, activation of Toll-like receptors (TLRs) and nucleotide-binding oligomerizations domain (NOD) like receptors (NLRs), propagating on-going inflammation. Mitochondrial DNA (mtDNA) is particularly susceptible to oxidative damage due to its close proximity to the site of ROS production and the lack of protective histones.[150] The accumulation of mutations alter the expression of respiratory complex subunits and thus OXPHOS efficiency, creating a positive feedback response with further ROS release, mitochondrial damage and inflammation.[22] Several mechanisms have been attributed to mitochondrial ROS-mediated inflammation, including activation of tumour necrosis factor receptors (TNFRs) and NOD, Leucine Rich Repeat And Pyrin-Domain Containing-3 (NLRP3) inflammasome signals. This activation of the inflammasome triggers pro-inflammatory cytokines, which are directly driven by mitochondrially mediated ROS and DAMPs, such as mtDNA, extracellular ATP and nuclear histones.

Fig 4. Perioperative redox balance

The delicate balance between ROS production and removal (affecting redox regulation) during surgery, mediated by a variety of factors, many of which are modifiable during the perioperative period.